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Preparation and complete ^{1}H and ^{13}C assignment of some pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (PCUD) derivatives.

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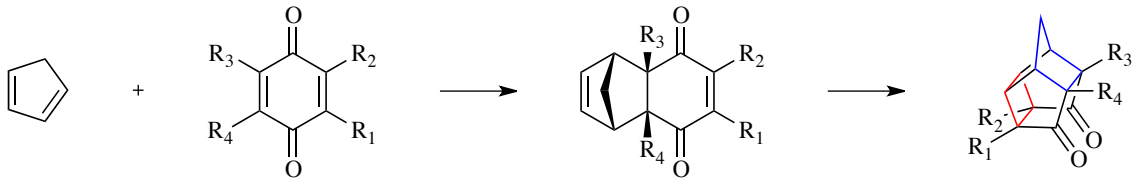
Graphical Abstract



Abstract

The preparation of a number of alkyl and alkoxy derivatives of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane- 8,11-dione derivatives utilising a cheap, practical, low energy, "green", single-pass continuous flow photochemical reactor is reported Their ^{1}H and ^{13}C NMR spectra are fully assigned, revealing some general characteristics not previously reported for this class of compound, which should aid the assignment and prediction of the NMR spectra of new PCUD derivatives.

Introduction

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane- 8,11-dione derivatives (PCUD's) are an interesting group of molecules prepared by the photochemical isomerization of the product of a Diels-Alder reaction between a cyclopentadiene and a 1,4-benzoquinone molecule (Figure 1). With the ready availability of both substituted benzoquinones and substituted cyclopentadienes a wide variety of derivatives have been prepared and studied.[1-6] The archetypal molecule is the unsubstituted diketone **1p**, first prepared by Cookson from the [2+2] photocyclisation of tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione **1t**, which encompasses a series of two five membered rings (black) bridged with a four membered ring (red) and a further five membered ring (blue) (Figure 1). These pentacyclic structures have been incorporated into many molecules capable of antifungal and antibacterial

activity,[7] HIV protease inhibition[8] and anti-inflammatory activity.[9] As a direct result of their importance, research on PCUD derivatives continues to the present day.[10-12] However, while NMR data for this class of compound is reported extensively in the general synthetic literature, in many cases a detailed assignment of the data is missing. This is understandable as much of the work pre-dates both the widespread availability of high-field spectrometers (^{1}H at 500 MHz or greater) and the common use of two-dimensional experiments. Furthermore, the challenge of assignment is increased by the relatively narrow range of frequencies for ^{1}H and ^{13}C signals other than the carbonyl carbons in the final cage structure, coupled with the limitations of additivity rules when applied to strained polycarbocyclic systems. Herein we report an improved synthesis of a number of PCUD derivatives, which we characterise fully by assigning their ^{1}H and ^{13}C spectra. While analysing the NMR spectra we were able to note some general trends that we will highlight to aid the future analysis of new PCUD derivatives.

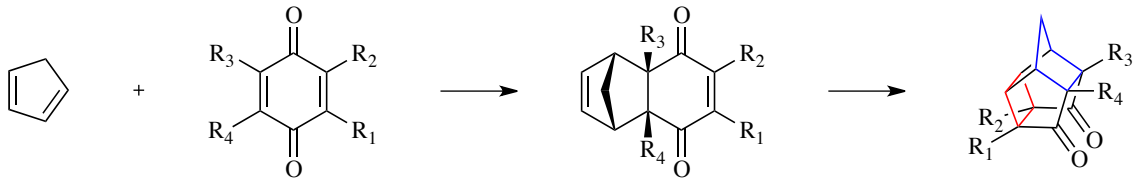


Figure 1: General synthesis of substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane- 8,11-diones

Results and Discussion

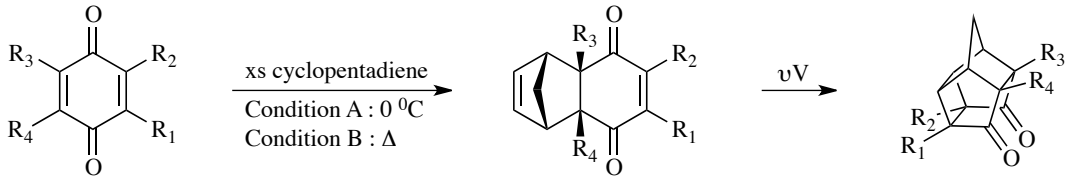
Design and construction of the continuous flow photoreactor

Photochemical flow reactors have been exploited in synthesis, most notably by the Booker-Milburn group who redesigned a classic batch reactor, consisting of a double walled vessel cooled on the outside, with a central Pyrex or quartz glass "finger" containing a high power medium pressure mercury lamp, by wrapping the immersion well with 3 layers of FEP tubing and connecting this to an HPLC pump. This setup overcame the limitations of batch reactors by providing a continuous flow of reagents, over a large surface area, close to the UV source, to enable large quantities of photolysed products to be produced.[13] However, the use of a specialised mercury lamp producing high intensity UV light results in high-energy use (400W) and additional health and safety considerations.

In view of this, we designed and built a new flow photoreactor satisfying the following criteria; 1. low cost; 2. low energy consumption; 3. easy to build and repair; 4. operating close to ambient temperature; 5. capable of generating useful amounts PCUD's in a relatively short time. Our reactor is designed around two domestic "energy saving" 20W UV light bulbs, which are considerably

cheaper than a mercury lamp and consume approximately 40W of energy. These are surrounded by 10 m of PFA tubing (0.8 mm i.d. x 1.6 mm o.d.) in a figure of eight format. PFA tubing possesses excellent UV transmission properties, similar to FEP, while the figure of eight format enabled maximum exposure of the material to the UV source.[13] To complete the cell, two external fans working cooperatively provided adequate cooling (< 29 °C) to enable the whole set up to be housed in a readily available, inexpensive plastic box, coated in reflective foil. (Further information about the construction of the flow reactor, the overlap of its emission profile with the absorption spectrum of various substrates, and the rate of conversion of **1t** to **1p** is provided in figures in electronic supplementary information).

For purposes of evaluation of the photoreactor, synthesis began with the Diels-Alder reaction of cyclopentadiene and 1,4-benzoquinone to give **1t** as a model compound. The Diels-Alder reaction of an excess of freshly prepared cyclopentadiene with benzoquinone proceeded smoothly at 0 °C to provide a large quantity of **1t**. For comparison, a classical "batch" photocyclisation utilising a medium pressure UV light source was undertaken. Dissolution of **1t** in acetone and exposure to the UV lamp source enabled 0.5 g to be converted to the desired product **1p** ("Cookson's dione") in 6 h. Clearly, with a number of substrates to be processed, a faster procedure was desirable, hence our decision to develop a flow reactor. Gratifyingly, after some optimisation of conditions using the flow reactor, we were able to develop a system that allowed 0.5 g of **1t** to be converted to **1p** in 30 minutes. With a reliable synthetic sequence in place subsequent reactions between substituted quinones and cyclopentadiene proceeded smoothly to produce **2t** – **6t** and **8t** in good overall yields (Table 1).



1t - 7t **1p - 7p**

Entry	R_1	R_2	R_3	R_4	Conditions	% Yield tricyclo cpd	% Yield pentacyclo cpd
1	H	H	H	H	A	70 **(1t)**	60 **(1p)**[a]
2	Me	H	H	H	B	99 **(2t)**	96 **(2p)**
3	Me	H	Me	H	B	97 **(3t)**	99 **(3p)**
4	Me	H	H	Me	B	99 **(4t)**	64 **(4p)**
5	*i*-Pr	H	Me	H	B	96 **(5t)**	52 **(5p)**
6	OMe	OMe	Me	H	B	92 **(6t)**	99 **(6p)**
7	Me	Me	H	H	B	**(7t)**[b]	**7p**[b]

8	OMe	H	H	H	B	98 **(8t)**[b]	98 **8p**[b]

[a] data also reported and assigned [14, 15]; [b] data reported, but not assigned[5], Okamoto et al

Table 1: Synthesis of pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane- 8,11-dione derivatives.

With a robust synthetic pathway in place, NMR analysis of **1p** was undertaken (Tables 2 and 3, respectively).[16] As the ^{1}H NMR spectrum of **1p** allows little analysis due to its symmetry, the ^{13}C shifts were analysed revealing that the shifts of the methine carbons are principally determined by two factors. The first is the proximity of the methine carbon to a junction that involves a 4-membered ring, as the effect of small rings in moving carbon shifts to lower frequencies is well documented and, although it is most pronounced for 3-membered rings, is still significant for 4-membered rings.[17] The second factor is the methine's proximity to a carbonyl group. Taking these factors into account, an order for the methine carbon shifts in **1p** (from high to low frequency) can be presented as C_{9+10} (α to carbonyl at junction of 5- and 6-membered rings), C_{3+5} (β to carbonyl at junction of 5-membered rings), C_{1+7} (α to carbonyl at junction of 4- and 5-membered rings), and C_{2+6} (β to carbonyl at junction of 4- and 5-membered rings). In contrast, the methylene bridge (4-C) is easily identified either by multiplicity editing (Figure 2, blue signals) or, historically, by off-resonance decoupling.

Having established an understanding of the ^{13}C shifts for **1p**, relating this trend to the alkyl-substituted derivatives **2p** – **6p** is less straightforward. The alkyl substitution pattern is, as expected, clearly determined by steric considerations in the Diels-Alder reaction to produce the intermediates **2t** – **6t**. However, once the symmetry of the pentacyclo product is reduced by substitution, the difficulty of assignment increases considerably. This difficulty arises partly because of the limited chemical shift range of the methine carbon signals, but also because attempts to predict chemical shifts relative to **1p** on the basis of simple increment effects[18] are not sufficiently accurate to be useful even after geometry dependent γ terms have been incorporated.[19, 20] One reason for this may be the extent to which the electronic structure of the fused 4- and 5-membered ring systems differs from the normal sp^3 hybridization found in linear alkanes and larger ring systems. Evidence to support this comes from the size of the $^{1}J_{C\text{-}H}$ coupling constants in **2p**, measured from a ^{13}C spectrum acquired without ^{1}H decoupling. This reveals that all the methine carbons have $^{1}J_{C\text{-}H} > 140$ Hz, which is considerably larger than the average value of around 126 Hz in linear alkanes. The size of the $^{1}J_{C\text{-}H}$ has been phenomenologically linked to the hybridization of the C-H bond with the initial observation that the % of s character is approximately equal to 0.2 * $^{1}J_{C\text{-}H}$, and, while there has been subsequent refinement of the concept,[21] the basic rule of thumb still holds as an approximation. While it is perhaps not too surprising that the methine groups α to carbonyls should

show some sp^2 character, due to keto-enol tautomerism, this is not the case for the more remote methine carbons. Nevertheless, the $^1J_{C\text{-}H}$ of 156 Hz observed for C_{2+6} (β to carbonyl at junction of 4- and 5-membered rings) in **1p** is essentially the same as that observed in ethene, and is comparable to the value of 155 Hz observed in cubane,[22] but considerably higher than the value of 134 Hz reported for cyclobutane.[17] This suggests that the hybridisation in the fused ring system is significantly different than that in the isolated 4- or 5-membered rings, presumably to accommodate the necessary C-C bond angles.

Interpretation of the ^1H shifts is, in some respects, more difficult since the ^1H shifts in 4-membered rings have long been recognised as exceptional.[23] This can be seen by considering the ^1H shifts in cycloalkanes and the corresponding prismanes. These are given in Table 2, together with the corresponding ^{13}C shifts, $^1J_{CH}$ values and the strain energies for the simple cycloalkanes.

Compound	δ ^1H / ppm	δ ^{13}C / ppm	$^1J_{C\text{-}H}$ / Hz	Strain Energy / kJmol^{-1}
Cyclopropane	0.20 [24]	-2.8 [25]	160 [24]	115.1
Prismane [26]	2.28	30.6	180	
Cyclobutane [17]	1.94	23.3	134	110.1
Cubane [27]	4.03	47.7	155	
Cyclopentane	1.51 [28]	25.8 [25]	129 [25]	26.0
Pentaprismane [29]	3.84	48.6	148	

Table 2: Summary of characteristic NMR parameters for selected cycloalkanes and prismanes

The reference point for any discussion should be the shifts for cyclohexane, since the 6-membered ring has negligible strain energy. At the other extreme, we have cyclopropane , which has a large strain energy (115.1 kJmol^{-1}). Both the ^1H and ^{13}C shifts of cyclopropane are considerably to low frequency of the corresponding values for cyclohexane and the $^1J_{CH}$ is considerably higher. Cyclopentane has moderate strain energy and its ^1H and ^{13}C shifts are broadly similar to cyclohexane, with a small increase in the observed $^1J_{CH}$ value.

Cyclobutane does not fit any simple interpolation from the other small cycloalkanes. Its strain energy (110.1 kJmol^{-1}) is almost as big as that for cyclopropane; its $^1J_{CH}$ value is intermediate between cyclopropane and cyclopentane; its ^{13}C shift is significantly to low frequency of cyclopentane, as expected for a small ring. The somewhat surprising feature of the data is the ^1H shift of cyclobutane, which is considerably to high frequency of the corresponding shifts for cyclopentane and cyclohexane.

This observation carries through to the prismanes. The ^{1}H and ^{13}C shifts of each prismane are considerably to high frequency of the shifts for the corresponding cycloalkane, as expected. The ^{13}C shifts of the prismanes increase with ring size, but the ^{1}H shifts again show that the 4-membered ring species (cubane) resonates at significantly higher frequency than either the 3-membered ring species (prismane) or the 5-membered ring species (pentaprismane).

In the molecules studied in this paper, the protons in the 2 and 6 positions in the unsubstituted PCUD (that is the 4-membered ring protons furthest from the carbonyl groups) have the highest frequency shifts of all the methine protons. When the 1 position is substituted, either by an alkyl or a methoxy group, the hydrogen in the 2 position shifts to lower frequency and, in many cases, comes at a lower frequency that at least one of the bridgehead hydrogens in the 3 and 5 positions. However, in those molecules studied where there is no substituent at the 7 position, the hydrogen at the 6 position (remote from substitution) is always the highest frequency methine signal. The next highest frequency methine ^{1}H signal corresponds to either the 2 position, 3 position, or 5 position, but the ordering depends on the position and type of substituents at the 9 and 10 positions.

Alkyl substituents in these molecules shift the ^{1}H signal at adjacent positions to lower frequency, which is the opposite of the effect observed for ^{13}C signals. Indeed, it is notable that the relative shifts of the various methine protons generally show an opposite trend to the shifts of the carbons they are directly bonded to, as shown in Figure 2, so the highest frequency methine proton (6 position) corresponds to the lowest frequency methine carbon. This may be taken as a further indication of the unusual hybridisation present in these molecules.

Attempts to predict both the ^{1}H and ^{13}C shifts using modern commercially available software[30] are similarly unsatisfactory owing to the narrow range of methine shifts and the scarcity of related assignments in the literature. It is hoped that publication of some detailed assignments for this class of compounds will be useful in this regard.

Experimental

NMR spectra were recorded in $CDCl_3$ solutions at 298K on either a Varian VNMRS-600 or Varian VNMRS-700 spectrometer. For each sample, ^{1}H, ^{13}C, COSY, HSQC and HMBC spectra were acquired to allow complete assignment of the resonances. The HMBC spectra were optimized for $^{n}J_{CH}$ = 8Hz. Spectra were referenced to TMS using residual solvent signals as secondary standards.

Standard procedure for the formation of undeca-4,9-diene-3,6-diones

Substituted benzoquinones were dissolved in a minimum amount of dichloromethane (2 ml) and mixed with a large excess of freshly distilled cyclopentadiene. The resultant solution was either stirred at 0 °C or refluxed for 3 hours, warmed up or cooled down and then evaporated under reduced pressure. The residue was subjected to flash chromatography (*n*-hexane/Et_2O 1:0, 95:5, 9:1, 4:1, 7:3, 1:1) to afford the desired undeca-4,9-diene-3,6-diones. Full characterisation for each compound is provided in Electronic Supplementary Information.

Standard procedure for the production of undecane-8,11-diones

Substituted undeca-4,9-diene-3,6-diones (~500 mg) were dissolved in acetone (5 ml) and exposed to uV light (360 nm) using a flow system running at a rate of 0.16 ml/min. The solution was then evaporated under reduced pressure and subjected to flash chromatography (*n*-hexane/Et_2O 1:0, 95:5, 9:1, 4:1, 7:3, 1:1) to afford the desired pentacycloundecane-8,11-diones. Full characterisation for each compound is provided in Electronic Supplementary Information.

Acknowledgments

The authors gratefully acknowledge technical assistance from Rachel Fairbairn made possible by a Nuffield Foundation Bursary Placement.

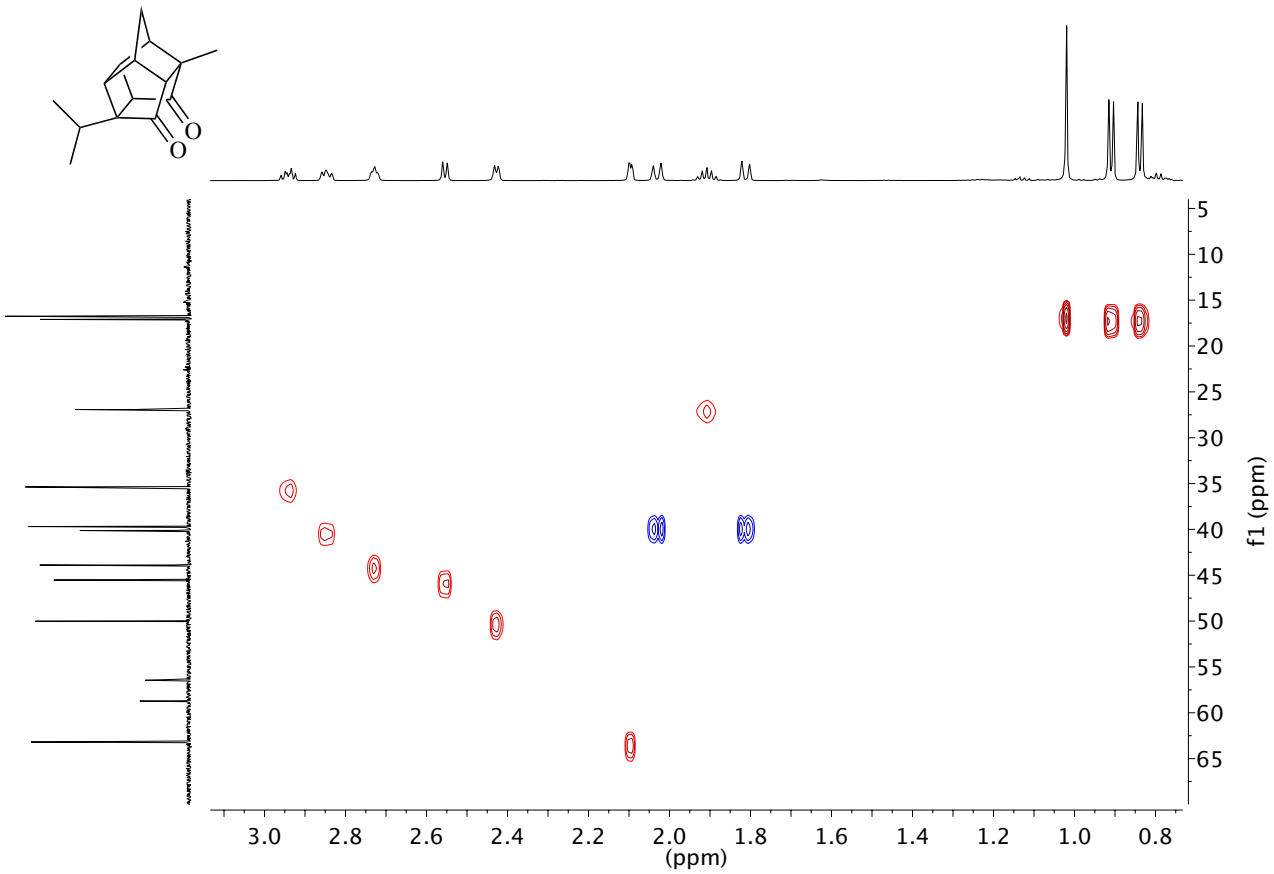
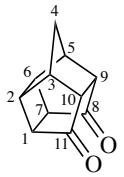
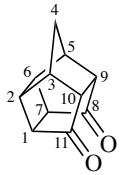


Figure 2: HSQC spectrum of **5p** showing the opposing trends in the ^{1}H and ^{13}C shifts of methines.



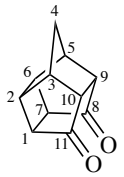
Proton	**1p**[a]	**2p**[b]	**3p**[b]	**4p**	**5p**	**6p**	**8p**[c]
1	2.81						
2	3.18	2.79	2.76	2.70	2.85	3.22	3.09
3	2.95	2.85	2.84	2.38	2.73	2.92	2.96
4s	2.05	2.03	2.08	2.04	2.04	2.10	2.04
4a	1.90	1.88	1.84	1.79	1.81	1.93	1.95
5	2.95	2.91	2.49	2.84	2.43	2.53	2.93
6	3.18	3.14	3.09	3.06	2.94	3.22	3.26
7	2.81	2.36	2.41	2.28	2.55		2.88
9	2.71	2.66		2.09			2.71
10	2.71	2.72	2.20		2.10	2.14	2.64
		1-Me, 15.8	1-Me, 1.17	1-Me, 1.15	1-^{i}Pr, 0.84, 0.91, 1.91	1-OMe, 3.57 or 3.58	1-OMe, 3.46
			9-Me, 1.08	10-Me, 1.04	9-Me, 1.02	7-OMe, 3.57 or 3.58	
						9-Me, 1.11	



Carbon	1p[a]	2p[b]	3p[b]	4p	5p	6p	7p[b]	8p[c]
1	43.8	48.4	48.1	47.7	56.4	83.4 or 83.5	50.1	82.0
2	38.8	45.0	44.3	43.9	40.2	41.1 or 41.2	43.4 or 44.2	43.3
3	44.7	43.7	44.0	49.5	44.0	43.8	43.4 or 44.2	43.9
4	40.5	40.9	39.5	39.9	39.7	41.3	41.2	41.9
5	44.7	44.5	50.0	44.6	50.1	49.4	43.4 or 44.2	43.8
6	38.8	36.2	34.9	35.5	35.5	41.1 or 41.2	43.4 or 44.2	34.6
7	43.8	50.3	49.8	50.0	45.7	83.4 or 83.5	50.1	48.5
8	212.1	212.2	213.9	212.4	214.6	211.0	213.7	209.6
9	54.7	54.5	58.2	62.0	59.7	54.8	54.7	54.7
10	54.7	54.7	61.4	58.4	63.3	58.5	54.7	50.8
11	212.1	212.8	213.0	214.5	212.9	209.4	213.7	210.6
		1-Me, 15.8	1-Me, 15.6	1-Me, 15.9	1-^{i}Pr, 17.1, 26.9	1-OMe, 54.8	1-Me, 11.4	1-OMe, 53.5
			9-Me, 16.8	10-Me, 17.1	9-Me, 16.8	7-OMe, 54.8	7-Me, 11.4	
						9-Me, 16.5		

[a] previously reported[6, 14, 15]; [b] previously reported but not assigned[3, 6]; [c] previously reported but not assigned[3, 6]

Table 3: ^{13}C chemical shifts of some PCUD derivatives



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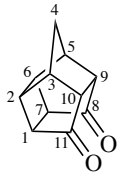
4s	2.05	2.03	2.08	2.04	2.04	2.10	2.04
4a	1.90	1.88	1.84	1.79	1.81	1.93	1.95
5	2.95	2.91	2.49	2.84	2.43	2.53	2.93
6	3.18	3.14	3.09	3.06	2.94	3.22	3.26
7	2.81	2.36	2.41	2.28	2.55		2.88
9	2.71	2.66		2.09			2.71
10	2.71	2.72	2.20		2.10	2.14	2.64
		1-Me, 15.8	1-Me, 1.17	1-Me, 1.15	1-^{i}Pr, 0.84, 0.91, 1.91	1-OMe, 3.57 or 3.58	1-OMe, 3.46
			9-Me, 1.08	10-Me, 1.04	9-Me, 1.02	7-OMe, 3.57 or 3.58	
						9-Me, 1.11	



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2	38.8	45.0	44.3	43.9	40.2	41.1 or 41.2	43.4 or 44.2	43.3
3	44.7	43.7	44.0	49.5	44.0	43.8	43.4 or 44.2	43.9
4	40.5	40.9	39.5	39.9	39.7	41.3	41.2	41.9
5	44.7	44.5	50.0	44.6	50.1	49.4	43.4 or 44.2	43.8
6	38.8	36.2	34.9	35.5	35.5	41.1 or 41.2	43.4 or 44.2	34.6
7	43.8	50.3	49.8	50.0	45.7	83.4 or 83.5	50.1	48.5
8	212.1	212.2	213.9	212.4	214.6	211.0	213.7	209.6
9	54.7	54.5	58.2	62.0	59.7	54.8	54.7	54.7
10	54.7	54.7	61.4	58.4	63.3	58.5	54.7	50.8
11	212.1	212.8	213.0	214.5	212.9	209.4	213.7	210.6
		1-Me, 15.8	1-Me, 15.6	1-Me, 15.9	1-^{i}Pr, 17.1, 26.9	1-OMe, 54.8	1-Me, 11.4	1-OMe, 53.5
			9-Me, 16.8	10-Me, 17.1	9-Me, 16.8	7-OMe, 54.8	7-Me, 11.4	
						9-Me, 16.5		

[a] previously reported[6, 14, 15]; [b] previously reported but not assigned[3, 6]; [c] previously reported but not assigned[3, 6]

Table 3: ^{13}C chemical shifts of some PCUD derivatives

References

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